B Cell Compartmental Features and Molecular Basis for Therapy in Neuromyelitis Optica Spectrum Disorder

Short title：B cell landscape in NMOSD

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ABSTRACT

Background: To characterize B cell programming towards autoimmunity across different compartments in patients with neuromyelitis optica spectrum disorder (NMOSD).

Methods: We characterized B cell transcriptomic profiles via single-cell RNA sequencing across the blood, bone marrow and cerebrospinal fluid (CSF) in patients with NMOSD.

Results: Four major subpopulations of B cells with distinct signatures across the tissues were identified: naïve B cells, memory B cells, autoimmune B cells, and antibody secreting cells (ASCs). NMOSD B cells show proinflammatory activity with an increased expression of chemokine receptor genes (*CXCR3* and *CXCR4*). Blood B cells display an increase of antigen presentation markers (*CD40* and *CD83*), as well as activation signatures (*FOS*, *CD69* and *JUN*). In contrast, bone marrow contains a large ASCs pool with increased oxidative and metabolic activity reflected by *COX* genes and ATP synthase genes. Typically, NMOSD B cells become hyper-responsive to type I interferon, which facilitates B cell maturation and anti-aquaporin-4 autoantibody production. The fraction of antibody secreting cells (ASCs) was significantly elevated in NMOSD. Both $CD19^-$ and $CD19^+$ ASCs could be ablated by tocilizumab but not rituximab treatment in NMOSD.

Conclusion: B cells are compartmentally fine-tuned towards autoreactivity in NMOSD. Inhibition of type I interferon pathway may provide a new therapeutic avenue for NMOSD.